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Diuertic effect of L-threo-3,4-dihydroxyphenylserin, a noradrenaline precursor, in rats and mice

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L-Threo-DOPS, a noradrenaline (NA) precursor, produced a dose-dependent increase in the volume of urine in mice and rats. It also increased the total output of sodium and chloride ions, but not the excretion of potassium ion. Treatment with peripheral decarboxylase inhibitors antagonized not only the diuretic action, but also the increase in the concentration of kidney NA produced by L-threo-DOPS. These results suggest that the diuretic action of L-threo-DOPS might not be due to its direct action, but largely to NA formed by its decarboxylation in the kidney.

The synthetic amino acid, 3,4-dihydroxyphenylserine (DOPS) is an immediate precursor of noradrenaline (NA). It has also been shown that DL- or L-threo-DOPS can be decarboxylated by aromatic L-amino acid decarboxylase to form NA in-vitro (Inagaki & Tanaka 1978) and produce an increase of NA in the brain and peripheral tissues such as plasma or heart in mice, rats or man (Bartholini et al 1975; Suzuki et al 1982; Nakamura et al 1984).

L-Threo-DOPS produces a positive chronotropic effect in rat atrial preparations (Araki et al 1978) and a slow-onset and long-lasting hypertensive effect in rats (Araki et al 1981). Clinically L-threo-DOPS has beneficial effects on orthostatic hypotention in patients with familial amyloid polyneuropathy (Suzuki et al 1982) or in parkinsonian patients (Birkmayer et al 1983), and also on akinesia and freezing phenomena in parkinsonian patients (Narabayashi et al 1981).

In the present study we have demonstrated a marked diuretic effect of L-threo-DOPS in rats and mice.

Methods

Male dd strain mice, 23 to 27 g, and male Wistar rats, 100 to 200 g, were used. All experiments were performed at 24 ± 1 °C and a relative humidity of 55 ± 5%.

For 18 h before testing animals were allowed no food but had free access to water. They were divided at random into groups of 10 mice or 3 rats and were placed in metabolism cages. Saline at 37 °C, 2·5 ml/100 g weight, was given orally, followed immediately by L-threo-DOPS in 0·5% methylcellulose (MC) solution, 1 ml/10 g weight; a similar volume of 0·5% MC solution was given to controls. Benserazide, or carbidopa (3 mg kg^{-1}), was administered with L-threo-DOPS in solution. Urine volumes were recorded for 3 h after L-threo-DOPS. Urine sodium and potassium ions were determined by flame photometry and chloride by the method of Zall et al (1956).

Rats were decapitated 1 h after the injection of L-threo-DOPS. Kidneys and hearts were quickly removed, and the tissues homogenized with 3 ml of ice-cold 0·4 M perchloric acid. After centrifugation of the homogenates, the supernatants were adjusted to pH 7·5 with 1 M ammonium phosphate buffer (pH 7·5) and applied to a column of boric acid gel. NA and DOPS were eluted by the method of Suzuki et al (1982) and detected by the means of HPLC techniques.

Results

L-Threo-DOPS produced a dose-dependent increase in the volume of urine in rats (Fig. 1). The duration of the diuretic response was also dose-dependent. This effect began within 20 min of injection of L-threo-DOPS and the peak effect was observed within 60 min. In mice, L-threo-DOPS also caused a rapid increase in urine flow (Fig. 1) but its diuretic potency was lower in mice. The effects of L-threo-DOPS on excretion of electrolytes in rats are shown in Table 1. The total output of sodium ion was markedly increased at a diuretic dosage of L-threo-DOPS (30 mg kg^{-1}). It also produced a significant increase in the total output of chloride ion, but not in the excretion of potassium ion. The treatment with benserazide or carbidopa (3 mg kg^{-1}) significantly

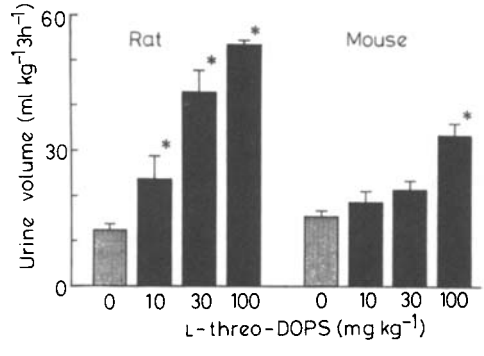

FIG. 1. Diuretic effect of L-threo-DOPS in rats and mice. L-Threo-DOPS was administered orally at doses of 0, 10, 30 and 100 mg kg^{-1}. Spontaneously voided urine was collected for 3 h after. Vertical bars show the s.e. of 5 groups of 3 rats or 10 mice. *$P < 0·05$ when compared with vehicle group (Student's t-test).

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Table 1. Effect of benserazide and carbidopa on renal excretion of water and electrolytes, and on the kidney and heart concentrations of noradrenaline in L-threo-DOPS-treated rats.

Drugs	Urine volume (ml kg^{-1} 3 h^{-1})	Electrolytes (mequiv. kg^{-1} 3 h^{-1}) Na^+	K^+	Cl^-	Noradrenaline (μg g tissue^{-1}) Kidney	Heart
0·5% Methylcellulose	15·9 ± 1·8	1·27 ± 0·12	0·41 ± 0·05	1·42 ± 0·10	0·17 ± 0·01	0·98 ± 0·04
L-Threo-DOPS	51·9 ± 3·0*	3·52 ± 0·15*	0·54 ± 0·03	3·12 ± 0·24*	1·80 ± 0·35*	1·00 ± 0·06
Benserazide + L-threo-DOPS	20·4 ± 0·8†	1·56 ± 0·09†	0·51 ± 0·06	1·75 ± 0·07†	0·30 ± 0·03†	0·85 ± 0·21
Carbidopa + L-threo-DOPS	13·7 ± 2·1†	1·12 ± 0·12†	0·33 ± 0·04	1·13 ± 0·22†		

Benserazide and carbidopa at 3 mg kg^{-1} were administered orally at the same time with L-threo-DOPS (30 mg kg^{-1} p.o.). Total urine volumes and electrolyte concentrations excreted 3 h following drug administration. Concentrations of noradrenaline were measured 1 h after drugs. Each value represents the mean ± s.e. (n = 5).

*$P < 0·05$ when compared with vehicle group (Student's t-test). †$P < 0·05$ when compared with L-threo-DOPS group (Student's t-test).

antagonized the increase in urine volume and the total outputs of sodium and chloride ion (Table 1). These inhibitors alone produced no effect on the urine volume and electrolyte excretion.

After administration of L-threo-DOPS at 30 mg kg^{-1}, its concentration in kidney (20·5 ± 4·4 μg g^{-1}) was eight times higher than that in heart (2·8 ± 0·5 μg g^{-1}). L-Threo-DOPS produced a significant increase in the NA concentration in the kidney, but not in the heart (Table 1). The increase in the kidney NA was abolished by benserazide.

Discussion

We have shown that, on oral administration, L-threo-DOPS has a marked diuretic action in rats and mice. It also produced an increase in total output of both sodium and chloride ion at diuretic dosages but the total amount of potassium ion excretion was much smaller. The diuretic action occurred at relatively small doses compared with the other pharmacological effects of L-threo-DOPS. Redmond et al (1975) reported that intravenous injection of DL-threo-DOPS, at doses up to 200 mg kg^{-1}, produced no significant change in cardiac rhythmn, rate or mean blood pressure in unanaesthetized cats. Araki et al (1981) showed that, at 50 mg kg^{-1}, L-threo-DOPS produced a slight elevation in blood pressure in rats. The effects of L-threo-DOPS on the central nervous system have been reported to occur at fairly high doses (200–800 mg kg^{-1} i.p.) in mice (Nakamura et al 1984).

L-Threo-DOPS increased the concentration of NA in kidney much more than in heart. Treatment with peripheral decarboxylase inhibitors, such as benserazide or carbidopa, antagonized not only the increase in the concentration of kidney NA, but also the diuretic action induced by L-threo-DOPS. These results suggest that the diuretic action might not be due to its direct action, but largely to NA formed by decarboxylation of L-threo-DOPS in the kidney. It has also been shown that intraveneous or subcutaneous injection of NA produces diuresis in rats (Green & Sim 1961). Various possible mechanisms of the diuretic action of NA have been proposed (see, e.g. Schrier & Berl 1973): (1) an increase in glomerular filtration, (2) suppression of endogenous vasopressin (ADH) release, (3) an inhibitory effect of NA on the water permeability at the tubular epithelium by antagonizing ADH action. Though the mechanism of the diuretic action of L-threo-DOPS is thought to be similar to that of NA, there are some differences. In contrast to the fast onset and short duration effect of NA, L-threo-DOPS administered orally is gradually absorbed and gives rise to the increase of NA concentrations in the peripheral tissues.

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